Cardiovascular responses in prolonged hypothermia

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POPOVIC, V. P., AND KENNETH M. KENT. Cardiovascular responses in prolonged hypothermia. Am. J. Physiol. 209(6) : I069--I074. 1965.—Rats cooled to a body temperature of 15 C live for 9--10 hr. However, they do not survive the rewarming if the hypothermia has lasted more than 5 hr. Neither the cause of death in hypothermia after 10 hr, nor the cause of resuscitation failure of animals rewarmed after 5 hr in hypothermia is known.

In 31 rats cooled to and maintained at a body temperature of 15 C, cardiac output decreased continually during the entire period of hypothermia, having by the end of hypothermic survival the value of only 25% of output at the beginning of the hypothermic period. The arteriovenous differences of O2 content increased, while total peripheral resistance increased continuously during this time. During the 10 hr of hypothermic survival the hematocrit ratio rose from 42 to 65-70 vol %. Because of these changes it is suggested here that the failure of circulation is the probable cause of death in hypothermia.

cardiac output; survival time; oxygen consumption; blood oxygen content; arterial blood pressure; total peripheral resistance; muscle blood flow; white rat

Fifteen years ago cooling to a body temperature of 15--20 C was believed to be lethal for most homeotherms (1), but recent advances in cooling techniques permit human beings to be cooled to a much lower rectal temperature and to be successfully rewarmed (14). Some adult homeotherm animals can survive a body temperature close to the freezing point (4, 13). Newborn mammals survive even body cooling to a temperature of minus 8 C (21). Although the depth of hypothermia does not seem to represent a limiting factor for successful rewarming from hypothermia, the period a homeotherm can endure the hypothermic state is rather limited: the lower the body temperature, the shorter the time of survival becomes (15, 16). For instance, while adult rats cooled to a body temperature of 20--22 C survive 24 hr (6), rats cooled to 15 C survive only 9--10 hr (17). When animals are cooled to a body temperature of 2--8 C, the survival time is decreased to only 1.5 hr (2). But to survive permanently after being brought back to euthermia, a cooled animal has to be rewarmed during the first half of its hypothermic period. Thus, while a rat lives 9-10 hr when cooled to a body temperature of 15 C ("clinical survival"), it can be revived only if rewarmed during the initial 5 hr ("biological survival"). When rewarming is attempted after hypothermia lasting for 5 hr or more, the rat will die as soon as its body temperature reaches 25--20 C (17, 18).

The cause of death of mammals in prolonged hypothermia is not known. It is not known either why a hypothermic animal will die when rewarming is performed during the second part of its hypothermic period but would live for several more hours when hypothermia is preserved. A marked hemoconcentration of the blood (18) and a decrease of the arterial blood pressure (15), appearing after hypothermia has lasted for several hours, might be indicators of failing cardiovascular functions. This cardiovascular failure might then become the limiting factor which would prevent successful rewarming from hypothermia. To investigate this problem, cardiac output and related data were measured in hypothermic rats whose body temperature was decreased to 15 C and kept at this level as long as they lived.

METHODS

Thirty-one adult male rats (Sprague-Dawley) weighing 268--340 g were used in the experiments.

Cannulation of aorta and right ventricle of the heart. The aorta and the right ventricle of each rat were cannulated by polyethylene tubes (i.d. 0.28 mm), as described elsewhere (20, 22). The cannulation took place 10--20 days before the experiment to avoid the effects of acute surgery and anesthesia (19).

Cooling of the animal and maintaining body temperature at 15 C. All animals were cooled to a colonic temperature...
of 15°C by the hypercapnic hypoxic technique of Giaja (9). After being cooled to 15°C each animal was placed into a glass cylinder submerged in a water bath (Fig. 1). The temperature of the animal was maintained throughout the experiment at 15.2 ± 0.2°C by regulating the temperature of the water bath. The body temperature of the animal was recorded by two 40-gauge copper-constantan thermocouples and a multipoint potentiometric recorder (Honeywell). One thermocouple was inserted deeply in the esophagus and the other in the colon. In some experiments a deep-core temperature was additionally measured by a 40-gauge thermocouple implanted in the supramediastinal area at the time of the cannulation of the aorta and the right ventricle. In those experiments the leads from the thermocouples were exteriorized together with both cannulas at the neck of the animal and later connected to the recorder.

Survival time. The survival time was counted from the moment the body temperature of the animal reached 15.5°C until the moment of cessation of the myocardial contraction which was established electrocardiographically as well as from pressure recordings.

Oxygen consumption. This was measured continuously by an open-circuit system (8) using a paramagnetic oxygen analyzer and wet test gas flowmeter. In addition a gas phase oxygen transducer (Chemtronics) with a chopper preamplifier was used to record oxygen tension in the air leaving the animal’s chamber. Simultaneously the airflow was recorded by a pneumotachograph (Schwarzer) (Fig. 1). In some experiments a closed system was used in which CO₂ was absorbed and oxygen was added by a spirometer. Both systems gave comparable results.

Cardiac output. This was determined by the direct Fick method. After the animal was cooled to the body temperature of 15.5°C, the tips of its implanted cannulas were cut off. The open cannulas were then connected by needle adapters to polyethylene tubes leading to the outside of the chamber. The tubes leading outside the chamber were of the same size as the implanted cannulas. Arterial and mixed venous blood was sampled by a Unita pump several times during an experiment. Each sampling lasted 5 min. The amount of blood withdrawn for one sample was 0.19 ml, enough to duplicate the determination of oxygen content of the blood and hematocrit ratio measurements. The withdrawn blood was replaced from a hypothermic donor which had spent as much time in hypothermia as the experimental animal. The oxygen content of blood was determined by the Roughton and Scholander technique (24).

Mean arterial blood pressure. Blood pressure was recorded by a pressure transducer (P23DC, Statham) and a polygraph recorder (Schwarzer).

Hematocrit ratios. Duplicate measurements of hematocrit ratios were made of all samples of the arterial and of the venous blood after a 5-min centrifugation (13,000 rpm).

Electrocardiogram. Standard limb leads on a polygraph recorder were used to record the electrocardiogram.

Blood flow through the muscles of the iliolumbar region. This was determined in 8 of the 31 animals. During these measurements the animals were covered with a small plastic chamber and were kept on ice covered with a plastic sheet. The body temperature of the animal, therefore, was less stable and less uniform than described earlier. The blood flow was measured by gravity drainage of the venous blood from the distal part of right iliolumbar vein through an implanted polyethylene tube.

**FIG. 1.** Apparatus for measuring oxygen consumption, cardiac output, and other related data of hypothermic animals whose body temperature was maintained stable throughout experiment.
and into a plastic receptacle under mineral oil. The volume of blood in the receptacle was kept constant by equalizing via a Sigmamotor pump the outflow of the blood into the proximal part of the right femoral vein and the inflow into the receptacle. The pump was calibrated volumetrically before and after each experiment. The volume of priming blood was 1.6 ml (Fig. 2).

Cardiac output and total oxygen consumption of the animal were determined at the same time as the iliolumbar blood flow.

**Oxygen content of the venous iliolumbar blood.** $O_2$ content was measured in blood which was sampled periodically from a side branch of the iliolumbar cannula (Fig. 2).

**Oxygen consumption of the iliolumbar muscles.** $O_2$ consumption was calculated from venous flow through the iliolumbar vein and from the difference in oxygen content between iliolumbar venous blood and systemic arterial blood.

**RESULTS**

**Survival time ("clinical survival time").** Survival time of rats at body temperature of 15°C ranged from 7.5 to 10 hr, the average survival time being 9.1 hr.

**Oxygen consumption.** The $O_2$ consumption of hypothermic rats was stable during the first 6-7 hr, then it began to decrease markedly though the body temperature remained unchanged. One or two hours before death, the oxygen consumption was usually only half of the value measured during the initial 6 hr, as illustrated in Fig. 3.

**Heart rate.** During the entire hypothermic period the heart rate remained essentially unchanged. After the initial cooling and a short equilibrium phase, the heart rate stabilized between 55-75 and then remained unchanged until just before the death of the animal. One to three cardiac arrhythmias per minute were observed during the entire period of hypothermic survival. The arrhythmias were usually premature ventricular contractions and second degree heart block. The occurrence of arrhythmias increased somewhat during the last hour of survival, just before death.

**Blood oxygen content.** Compared to the euthermic state, the arteriovenous difference of oxygen content was somewhat decreased immediately after the stabilization of body temperature of the animal at 15°C. However, as time progressed, the oxygen content of the arterial blood increased, whereas the oxygen content of venous blood decreased continuously (Fig. 3). The arteriovenous difference of oxygen contents of all hypothermic animals thus increased steadily, reaching 15$\%$ more during the last hour before death (Fig. 4).

**Cardiac output.** Immediately after cooling, cardiac output was about 20-25 ml/min, and it decreased steadily thereafter. One hour before death the cardiac output was only 4-5 ml/min, or about 25$\%$ of that observed initially at the same body temperature (Fig. 3).

The calculated stroke volume of rats at a body temperature of 15°C was 0.42 ± 0.04 ml, considerably above the values measured in euthermic animals. Whereas, throughout the duration of hypothermia, the heart rate did not change, the stroke volume decreased continuously. The stroke volume reached the value of only 0.15 ml during the last hour before death (Fig. 4).

**Mean arterial blood pressure.** The mean arterial blood pressure of rats kept at a body temperature of 15°C was
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DISCUSSION

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lochrome (11) and this phenomenon might contribute to a failing
circulation in hypothermic animals. A steadily increasing

FIG. 4. Arteriovenous difference of oxygen contents and calcu-
ulated stroke volume of 31 rats during 15°C hypothermia (mean
values and standard deviations).

70–75 mm Hg. This pressure remained unchanged during
the first 3–4 hr of cooling, then it began to decrease and just before death reached the value of 10–20 mm Hg.

Calculated total peripheral resistance. This increased con-
tinuously during the entire hypothermic period. If the calculated total peripheral resistance of euthermic ani-
imals was taken as being one, the peripheral resistance of rats during the 1st hr in hypothermia was 2.2. This
peripheral resistance increased steadily, reaching before
death the value of 3.6.

Hematocrit ratio. Immediately after the cooling, the
hematocrit ratio was similar to the control measurements.
The hematocrit ratio increased during the hypothermic
period, reaching 70 vol % just before death.

Muscle blood flow. The blood flow in the muscles de-
creased continuously during hypothermia. The decrease
of the regional blood flow through the iliolumbar muscles
was even greater than the decrease of the total-body
blood flow. The arteriovenous difference of oxygen con-
tents between the venous and the arterial iliolumbar
blood was somewhat greater than the whole-body arterio-
venous difference of oxygen contents. The oxygen con-
sumption of the muscles in the iliolumbar region de-
creased continuously during 8–10 hr of hypothermia,
until before death it was only 10 % of the initial value.

When a homeothermic animal is cooled to a body
temperature of 15–16°C and kept there for several hours,
its physiological characteristics change continuously,
some faster and others more slowly, until death super-
venes. However, the cause of death in hypothermia is still
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it is known that at a body temperature of 20°C the blood
flow in rat mesocerebi ceases in 90% of the small blood
vessels (3, 12). Closure of blood vessels might be expected
in those circumstances especially because of a further de-
crease in the cardiac output. Plasma skimming and trap-
pping of plasma in small vessels has also been observed
(11) and this phenomenon might contribute to a failing
circulation in hypothermic animals. A steadily increasing

events leading eventually to death. While the oxygen
consumption, arterial blood pressure, and heart rate
change little during several initial hours spent in hypo-
thermia, the viscosity of blood (already increased by the
cold) increases further because of hemoconcentration
(18). In this investigation it was shown that the cardiac
output is another parameter which changes profoundly
and continuously during prolonged hypothermia. The
cardiac output and the calculated stroke volume of
animals decrease continuously while the temperature of
the hypothermic animals remained constant. During the
same time the arteriovenous difference of oxygen con-
tents increased steadily. Thus the total O2 consump-
tion of the hypothermic animal remained unchanged during
the initial 4–5 hr. However, 5–6 hr after cooling began,
this compensatory mechanism—the increasing (a-v)O2
difference became inadequate. This happened when
circulation, after the animal spent several hours in hypo-
thermia, decreased below a critical level. The oxygen
consumption of the animal was then affected and from
this moment a continuous decrease was observed. Be-
cause of the shift in oxygen dissociation curves when
blood has a greater affinity for oxygen, this increased
(a-v)O2 difference is rather unexpected.

It is difficult to assess the cause of the continuously de-
creasing stroke volume observed in all our animals kept
in long term hypothermia. It is possible that the in-
creased heart work during the phase of the initially in-
creased stroke volume and during the initially increased
peripheral resistance might contribute to the circulatory
failure. Another possibility would be to associate the
continuously decreased stroke volume with a slowly fall-
ning hypothermic heart. Covino and Hannon (7) have
found that the diastolic ventricular excitability is greatly
depressed at low body temperatures. Furthermore,
Zimny and Gregory (25) found that in rabbits cooled to
a body temperature of 15°C there is an increased con-
version of ATP to ADP. Thus, it might be that an in-
adequate amount of ATP, brought forth by an inade-
quate metabolism or by an inefficient coupling, is the
basis of the myocardial failure and thus the beginning of
the vicious cycle which leads the hypothermic animals to
death. The third possibility would be to attribute the
continuously decreased stroke volume to a decreased
venous return. It has already been suggested that
venous return is inversely proportional to the viscosity
of the blood (10). In hypothermic animals it could be ex-
pected that an already decreased venous return would be-
come even smaller because of the hemoconcentration of
the blood and increased blood viscosity. Furthermore, it
is known that at a body temperature of 20°C the blood
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Successful rewarming, the hypothermic animal is still able to live for 3-4 hr longer because of this protective role of hypothermia. But, if rewarmed at this moment, the animal cannot be rewarmed successfully and it dies whenever its body temperature reaches 25-28 C because it entered a vicious cycle: rewarming of tissues brings about a sharp increase in O₂ needs which the already decreased circulation is not able to supply. An animal reaches during rewarming the maximal O₂ consumption at a body temperature of 28-30 C. An animal which spent more than 6 hr in 15 C hypothermia will, during rewarming, die at the same body temperature because of the apparent inability to supply enough oxygen to the tissues which were experiencing an oxygen debt for too long a period of time.

On the basis of our experiments, a cooled, nonhibernating mammal appears to suffer from a progressive failure of the circulation, characterized by a continuous decrease in cardiac output. The decrease in cardiac output is brought about by a continuously diminishing stroke volume uncompensated by an increase in heart rate. At the present time it is not possible to decide whether the first part in the chain of events leading to death is an increase in peripheral resistance brought about by a marked hemoconcentration, or failure of the myocardium itself, or decreased venous return. Whatever it is, this change reaches a critical point after the animal has spent 5-6 hr at a body temperature of 15-16 C. If external rewarming is applied after this moment the animal cannot be rewarmed successfully and it dies whenever its body temperature reaches 25-28 C.

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REFERENCES
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